

REMARKS

Claims 1-74 were pending prior to this Response, with claims 67-69 having been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b). By the present communication, no claims have been added or amended, and claims 41 and 71 have been amended. Claim 41 has been amended to correct informalities. Support for the amendment to claim 71 can be found throughout the application as filed. Specifically, support for the amendment can be found, for example, in step (g) of claim 71 as filed and at paragraphs 0075 - 0084. Accordingly, claims 1-66 and 70-74 are currently pending in this application.

Applicants have reviewed the rejections set forth in the Office Action mailed September 1, 2004, and respectfully traverse all grounds for the reasons that follow.

Objections to the Specification

The specification is objected to under 37 C.F.R. § 1.75(d)(1) for allegedly failing to provide proper antecedent basis for the subject matter of claims 12-13 and 46-47. Claims 12-13 and 46-47 are directed to a computer readable medium or media, or to a method, where a biochemical reaction network represents reactions occurring in a first cell and a regulatory data structure represents events occurring in a second cell of a population of cells. The population of cell can be a multicellular organism.

Sufficient antecedent basis for these claims is provided throughout the application. In particular, the application provides sufficient antecedent basis at, for example, paragraph 0033 where a regulatory reaction is defined in reference to a data structure to mean “a first reaction that is related to a second reaction by a function that alters the flux though the second reaction by changing the value of a constraint on the second reaction.” Further, the application describes reactants assigned to different compartments such as cells within a population when it teaches at paragraph 0038:

A plurality of reactants can be related to a plurality of reactions in any data structure that represents for each reactant, the reactions by which it is consumed or produced. . . . A data structure can include a first substrate or product in the

plurality of reactions that is assigned to a first compartment and a second substrate or product in the plurality of reactions that is assigned to a second compartment.

Still further, for example, the application describes at paragraph 0135 that the methods of the invention can be used to model a variety of organisms, including eukaryotic organisms, and expressly exemplifies the multicellular human organism. Paragraph 0136 additionally describes use of the methods of the invention to model events occurring in different cells of an organism when it describes that the methods can be used to simulate signal transduction and physiological systems. Both of these examples describe a biochemical reaction network representing reactions occurring in a first cell and a regulatory data structure representing events occurring in a second cell of a multicellular organism. For example, the methods of the invention can be employed to model interactions between signaling partners for signal transduction or to model physiological functions and events of organs, tissues or cells. In light of the above exemplary teachings, Applicants maintain that the application provides sufficient antecedent basis for claims 12-13 and 46-47 and respectfully request that this ground of objection be withdrawn.

Rejections under 35 U.S.C. § 101

Claims 1-33 stand rejected under 35 U.S.C. § 101 allegedly for being directed to non-statutory subject matter. The Office alleges that the claimed computer readable medium or media fails to impart functionality when employed as a computer component and is considered nonfunctional descriptive material. In this regard, the Office alleges that nonfunctional descriptive material recorded on a computer-readable medium is not statutory because it lacks a practical application and cites *In re Sarkar* as authority for this proposition.

Section 101 of Title 35 provides that any new and useful invention or discovery which is a process, machine, manufacture, or composition of matter qualifies as patentable subject matter. In holding that genetically modified bacteria was statutory subject matter, the Supreme Court in *Diamond v. Charkrabarty* concluded that Congress plainly intended a broad scope for patentable subject matter and that the enumerated categories in § 101 “include anything under the sun that is

made by man.” 445 U.S. 303, 308-09 (1980); *accord Diamond v. Diehr*, 450 U.S. 175, 182 (1981).

Claim 1 is directed to a computer readable medium or media which includes a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network where at least one reaction is a regulated reaction, and a constraint set for the plurality of reactions. The plain language of claim 1 places the claimed computer readable medium or media within the statutory categories enumerated in § 101. A computer readable medium is a thing and as such is a machine, manufacture or composition of matter.

The Office’s reasoning is that because the data structure contained on the computer readable medium or media lacks a practicable application it is precluded from statutory subject matter is unfounded. The inquiry of whether a claimed invention has a practicable application is relevant to computer related algorithms and business methods to separate abstract ideas, laws of nature and natural phenomena from patentable subject matter. *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F. 3d 1368, 1373-74 (Fed. Cir. 1998) (noting that the Freeman-Walter-Abele test for mathematical algorithm related inventions “has little, if any, applicability to determining the presence of statutory subject matter”). Here, a computer readable medium or media is neither an algorithm nor a business method. Rather, it is a thing and the inquiry proposed by the Office is irrelevant because “[a] claim drawn to subject matter otherwise statutory does not become nonstatutory simply because it uses a mathematical formula, computer program or digital computer.” *Id.* at 1375 (*quoting Diehr*, 450 U.S. at 187).

Further, the Office cites *In re Sarkar* for the proposition that merely claiming nonfunctional descriptive material stored in a computer-readable medium does not make it statutory, asserting that the claimed computer readable medium or media constitutes nonfunctional descriptive material allegedly because the data structure and data fail to impart functionality when employed as a computer component. However, the Office fails to provide a basis for the conclusion that the claimed computer readable medium or media containing the recited data structure is nonfunctional. The mere assertion that the claimed data structure fails to impart functionality lacks such a basis. Absent a reasoning why the claimed computer readable medium or media containing the recited data structure is considered to be nonfunctional, such broad conclusory statements fail to satisfy the Office’s burden for a proper rejection under § 101.

Further, while not conceding that the Office's application of a functional descriptive test or that *In re Sarkar* is applicable following *State Street* to the claimed computer readable medium or media or methods of the invention, the assertion that the claimed invention containing the recited data structure is nonfunctional is unfounded based on the plain language of the claim. First, the Office's own guidelines set forth certain views regarding the patentability of functional descriptive or nonfunctional descriptive material for computer related inventions and exemplifies a data structures stored on a computer readable medium to be patentable subject matter as functional descriptive material. M.P.E.P. § 2106 (IV)(B)(1). For example, the guidelines state:

When functional descriptive material is recorded on some computer-readable medium it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized. Compare *In re Lowry*, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035 (Fed. Cir. 1994) (claim to data structure stored on a computer readable medium that increases computer efficiency held statutory) and *Warmerdam*, 33 F.3d at 1360-61, 31 USPQ2d at 1759 (claim to computer having a specific data structure stored in memory held statutory product-by-process claim) with *Warmerdam*, 33 F.3d at 1361, 31 USPQ2d at 1760 (claim to a data structure per se held nonstatutory).

M.P.E.P. § 2106 (IV)(B)(1) (emphasis added). The guidelines further exemplify that works protected under copyright law such as music are nonfunctional descriptive material and do not become statutorily patentable merely by recording onto a compact disk. *Id.* Thus, the Office's own guidelines exemplify data structures to be statutory patentable subject matter when recorded on a computer readable medium.

Second, the guidelines further define a data structure, as well as a data structure considered to satisfy the Office's functional descriptive test and also define nonfunctional descriptive material to be:

Descriptive material can be characterized as either "functional descriptive material" or "nonfunctional descriptive material." In this context, "functional descriptive material" consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of "data structure" is "a physical or logical relationship among data elements, designed to support specific data manipulation functions." The New IEEE Standard Dictionary of Electrical and Electronics Terms 308 (5th ed. 1993).)

"Nonfunctional descriptive material" includes but is not limited to music, literary works and a compilation or mere arrangement of data. *Id.*

Thus, according to these definitions, a functional descriptive data structure is a relationship among data elements that imparts functionality when employed as a computer component.

The claimed computer readable medium or media containing the recited data structure falls within this definition and should be considered functional descriptive material and statutorily patentable. For example, the data structure is contained on a computer readable medium or media and therefore is a computer component. The claimed data structure also consists of a physical or logical relationship among data elements because it expressly claims relating a plurality of reactants to a plurality of reactions of a biochemical network. Further, the claimed computer readable medium or media containing the recited data structure also imparts functionality when employed as a computer component because is used to determine a systemic property of a biochemical reaction network.

In light of the above remarks, Applicants maintain that claims 1-33 are directed to statutory patentable subject matter and further has a practical application. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 1-66 and 70-74 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear how the data structure and constraint set are related to each other and the computer readable media. In this regard, the Office questions whether the claimed data structure and constraint set are on different disks; whether multiple copies are on a disk; whether an interaction exists between the data structure, constraint set and computer, and whether computer executable instructions were intended to be claimed.

Applicants submit that the claim as written is sufficiently clear to distinctly claim what Applicants regard as the invention. For example, claim 1 is directed to a computer readable medium or media having a data structure that relates a plurality of reactants to a plurality of reactions and a constraint set. As recited in the claim, the data structure and constraint set can be contained on a medium or on media so long as the data structure also specifies a relationship

between the plurality of reactants and reactions. Further, the terms data structure and constraint are defined in the application at, for example, paragraphs 0037 and 0048, respectively, and are used consistent with their art recognized meaning. In light of the plain language of the claim, the definitions set forth in the application and the recognized meaning of terms used in the claims, Applicants maintain that the claim is clear as written and withdrawal of this ground of rejection is respectfully requested.

Claims 2-7, 26-30 and 32-33 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because they are unclear and do not appear to further limit the computer readable medium or media of claim 1. The Office alleges that these claims appear directed to the value in the data structure or how the value is determined rather than modifying the structure of the data set or constraint set. In essence, the Office appears to allege that the claim is unclear because it does not change the structure of the claimed data structure or constraint set.

The second paragraph of § 112 requires that the claims be clear and concise to distinctly point out Applicants' claimed invention. While not conceding that the rejected dependent claims do or do not alter the structure of the claimed data structure or constraint set, Applicants respectfully point out that the terms of the claims are clear. In this regard, none of the terms or the claims as a whole appear to be imprecise, unclear or confusing. For example, claim 2 recites that the variable constraint of claim 1 is dependent upon the outcome of at least one reaction. The meaning of this claim is clear, in particular, the value of the variable constraint requires the outcome of a reaction. In the absence of a rationale as to why the rejected claims encompass more than one meaning, the Office has not met its burden. Accordingly, the claims are clear as written and withdrawal of this ground of rejection is requested.

Similarly, claims 9-13 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because they fail to limit the computer readable medium or media of claim 8. Applicants submit that claim 9 further limits the claimed computer readable medium or media of claim 8 because it recites that the regulatory data structure of claim 8 corresponds to any one of a variety of regulatory events including, for example, transcription of a gene, translation of an RNA, post-translational modification of a protein, inhibition of a protein, activation of a protein, assembly of a protein, change in pH, change in redox potential, change in temperature, passage

of time or degradation of a protein. Because these recited elements are not found in base claim 8, they are new to claim 9 and further limit the claim from which it depends. Similar newly recited elements also can be found in claims 10-13 and also further limit these dependent claims. In light of the additional recited elements, Applicants contend that the claims are sufficiently clear to satisfy the requirements of the second paragraph of § 112. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 8 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear what constitutes a representation of a regulatory event in the claimed regulatory data structure. Applicants submit that the meaning of the term “regulatory data structure” and its constituent elements are clear giving the meaning of the term as it is defined in the application. For example, the application sets forth that a regulatory data structure constitutes “a representation of an event, reaction or network of reactions that activate or inhibit a reaction, the representation being in a format that can be manipulated or analyzed.” Paragraph 0046. A data structure is defined at, for example, paragraph 0037 to mean a representation of information in a format that can be manipulated or analyzed and includes formats such as a list, a correlative matrix, sets of equations or sets of Boolean statements. The information included in these exemplary structures can be, for example, a substrate, product, reaction or a constraint placed on a reaction. The data structure and included information can be a representation of a reaction network such as a biochemical reaction network. Also, set forth are the meanings of the terms “biochemical reaction network” and “reaction” at paragraphs 0028 and 0031, respectively. In regard to a representation of a regulatory event, the application defines at, for example, paragraph 0047 the term “regulatory event” to mean a modifier of the flux through a reaction that is independent of the amount of reactants available to the reaction. Such modifications include a change in the presence, absence, or amount of an enzyme that catalyzes a reaction. Therefore, a regulatory event can be represented in a similar manner as other information in a data structure including formats such as lists, a correlative matrix, equations or Boolean statements. However, the information corresponding to a regulatory event references a modifier of the flux through a reaction. In light of the above definitions as well as other teachings throughout the application, Applicants submit that claims 9-13 are sufficiently clear to distinctly point out what Applicants

regard as the invention. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Claim 14 also stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the term “constraint function” is confusing as to whether it refers to an equation, data, executable instruction or command. If the term is intended to mean an executable instruction or command, the Office further alleges that it is unclear whether a constraint function is a program separate from the data structure and constraint set. Applicants submit that the term is sufficiently clear and definite to distinctly claim what Applicants regard as the invention. The meaning of the terms “constraint” and “function” are set forth in the application at, for example, paragraphs 0048 and 0049. As described therein, the term “constraint” refers to an upper or lower boundary for a reaction which can specify a minimum or maximum flow of mass, electrons, energy through a reaction or directionality. A boundary refers to a fixed or variable value. The term “function” is used consistent with its meaning in the computer and mathematical arts. For example, a function refers to a correspondence that assigns one element of one set to an element of the same or another set or a variable, such as a quality, trait, or measurement that depends on and varies with another. *Merriam-Webster Online Dictionary*. Merriam-Webster, 2005. <http://m-w.com/> (10 Feb. 2005). Further, for example, paragraph 0074 and Figure 3 exemplify functions as a logic statement. Thus, a function provides a correspondence between elements or variables. Claim 14 also specifies such a relationship because it recites that the constraint function correlates an outcome of a regulatory event with a variable constraint. In light of the descriptions in the application setting forth and exemplifying the meaning of the objected term as well as the plain meaning of the claim as written, Applicants maintain that the claim is sufficiently clear to satisfy the requirements of the second paragraph of § 112. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 19 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear how commands can be an optimization problem. Applicants submit that claim 19 is clear and definite as written. Base claim 17 recites commands for determining at least one flux distribution that minimizes or maximizes an objective function. Claim 19 further specifies that such commands for determining at least one flux distribution include an optimization problem. Further, optimization problems are described as a

mathematical representation at, for example, paragraph 0113. Solutions to such mathematical representations can be used for determining at least one flux distribution. Therefore, claim 19 includes commands for determining both at least one flux distribution as well as an optimization problem and is clear as written. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 20 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for use of the term “linear or nonlinear” allegedly because this term appears to embrace all types of optimization problems and fails to further limit claim 19. Applicants submit that claim 20 is clear as written and properly limits independent claim 19. For example, claim 19 is directed to commands having an optimization problem whereas claim 20 further specifies that the optimization problem includes a linear optimization problem or a nonlinear optimization problem. The National Institute of Standards and Technology defines an optimization problem to be:

A computational problem in which the object is to find the best of all possible solutions. More formally, find a solution in the feasible region which has the minimum (or maximum) value of the objective function.

National Institute of Standards and Technology. NIST 2005. <http://www.nist.gov/> (11 Feb. 2005) (citing *Algorithms and Theory of Computation Handbook*, pages 29-20 and 34-17, Copyright 1999 by CRC Press LLC. *Appearing in the Dictionary of Computer Science, Engineering and Technology*, Copyright 2000 CRC Press LLC. This definition includes problems that find a solution within a feasible region additional to linear and nonlinear optimization problems as well as other types of optimization problems. For example, a geometric optimization problem, defined as an optimization problem induced by a collection of geometric objects (*Id.*) constitutes one such optimization problem encompassed within the scope of claim 19 but distinguishable from claim 20. Therefore, claim 20 is clear and includes elements additional to claim 19. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 23 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly for use of the phrase “a set of linear algebraic equations.” The Office alleges that it is

unclear how this phrase represents a plurality of reactants to a plurality of reactions, questioning whether each equation represents a single reaction, the reactants or the products. Applicants submit that the phrase objected to is clear as written. The application describes at, for example, paragraph 0037 that a data structure of the invention can include a set of equations such as linear algebraic equations. Further, the application teaches at, for example, paragraph 0057 that a mathematical representation of the network can be generated using well known practices in the art from a list of reactions to create a data structure. Specifically exemplified is a list of dynamic mass balance equations for each metabolite that specifies its change in concentration over time as the difference between the rates of production and the rates of consumption of the metabolites by the various reactions in which it participates as a substrate or product. Also exemplified at, for example, paragraph 0057 is the conversion of these dynamic mass balance equations into a series of linear equations describing the balancing of metabolites in the network where five linear mass balance equations are set forth for the network exemplified in Figure 2A. The application further teaches at, for example, paragraph 0058 the inclusion of linear inequalities to represent reaction thermodynamics and concludes:

Collectively, these 5 linear equations and 7 linear inequalities describe the reaction network under steady state conditions and represent the constraints placed on the network by stoichiometry and reaction thermodynamics.

Paragraph 0059.

The above teachings as well as other descriptions throughout the application set forth with sufficient clarity and exemplify the meaning as well as how the phrase “a set of linear algebraic equations” represents a relationship between a plurality of reactants to a plurality of reactions to satisfy the requirements of § 112, second paragraph. Further, the above teachings as well as other descriptions throughout the application describe with particularity what elements are represented in a set of linear algebraic equations. Therefore, claim 23 is clear as written and withdrawal of this ground of rejection is respectfully requested.

Claim 30 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly for use of the term “confidence rating.” The Office merely states that it is unclear what this term references. Applicants submit that the term “confidence rating” is sufficiently clear to

distinctly claim what Applicants regard as the invention. For example, paragraph 0040 describes that a reaction represented in a data structure or model of the invention can be annotated to indicate a level of confidence with which a reaction is believed to occur in a particular biochemical reaction network or organism and that such information can be obtained during the course of building a metabolic reaction database. Further, the meaning of confidence level or a rating assigned thereto is well known in the art to mean the degree of certainty that an event will happen or that a statement is correct. In light of the above teachings in the application as well as the term's well accepted meaning in the art, Applicants maintain that claim 30 is sufficiently clear to satisfy § 112, second paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 34 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear whether the at least one flux distribution that minimizes or maximizes an objective function determined in step (e) corresponds to a systemic property. Claim 34 also stands rejected because the meaning of the term "objective function" is alleged not to be understood. Applicants respectfully draw the Office's attention to the last clause of step (e), which recites that the determination of the at least one flux distribution that minimizes or maximizes an objective function "thereby determine[s] a systemic property of said biochemical reaction network." In light of this express recitation that determination of at least one claimed flux distribution thereby determines a systemic property of the biochemical network, Applicants submit that the claims are clear and definite as written. Withdrawal of this ground of rejection is respectfully requested.

The term "objective function" is well known to those skilled in the art. In this regard, Applicants draw the Office's attention to the well known definition recited above for an optimization problem, which defines the problem as a solution which has a minimum or maximum value of the objective function. NIST 2005. <http://www.nist.gov/> (11 Feb. 2005) (*citing Algorithms and Theory of Computation Handbook*, pages 29-20 and 34-17, Copyright 1999 by CRC Press LLC. *Appearing in the Dictionary of Computer Science, Engineering and Technology*, Copyright 2000 CRC Press LLC. The meaning of an objective function is similarly well known in the art and is defined by the National Institute of Standards and Technology to mean "a function associated with an optimization problem which determines how good a

solution is.” *Id.* Further, Applicants have exemplified the meaning an objective function throughout the application. For example, the application teaches selecting and determining an objective function at paragraphs 0113 and 0114 when it states:

Objectives for metabolic function can be chosen to explore the ‘best’ use of the metabolic network within a given metabolic genotype. The solution to the above equation can be formulated as a linear programming problem, in which the flux distribution that minimizes a particular objective is found. Mathematically, this optimization can be stated as:

$$\begin{aligned} &\text{Minimize } Z \\ &\text{subject to } Z = \sum c_i \times v_i = \langle \mathbf{c} \bullet \mathbf{v} \rangle \end{aligned}$$

Where Z is the objective which is represented as a linear combination of metabolic fluxes V_i . The optimization can also be stated as the equivalent maximization problem; i.e. by changing the sign on Z .

This general representation of Z enables the formulation of a number of diverse objectives. These objectives can be design objectives for a strain, exploitation of the metabolic capabilities of a genotype, or physiologically meaningful objective functions, such as maximum cellular growth.

In light of the above, Applicants submit that the meaning of the objected term is well known in the art and is particularly described and exemplified in the application as filed. Accordingly, the term “objective function” is clear and withdrawal of this ground of rejection is respectfully requested.

Claim 35 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear whether this claim recites an active step to update a value in the constraint set. The Office also asserts that claims 35 and 36 are indefinite allegedly because it is unclear whether the outcomes of the at least one reaction in claim 35 or the regulatory event in claim 36 are information generated by the claimed method. Claim 37 is allegedly unclear because no time element is recited in base claim 34. Independent claim 34 recites providing a condition-dependent value to the claimed variable constraint. Claim 35 further recites that the value provided to the variable constraint changes in response to the outcome of at least one reaction in the data structure. Claim 36 further recites that the value provided changes in response to the outcome of a regulatory event. Claim 37 further recites that the value provided

changes in response to time. The application describes at, for example, paragraph 0049 that a variable constraint refers to a constraint that is capable of assuming any of a set of values in response to being acted upon by a function. Paragraph 0033 describes that a regulatory reaction refers to a first reaction that is related to a second reaction by a function that alters the flux through the second reaction by changing the value of a constraint on the second reaction.

Based on these definitions, claims 35, 36 and 37 further specify that the condition-dependent value provided to the variable constraint of claim 34 results from one or more reactions specified in the data structure, from a regulatory event or from a temporal event when acted on by a function that alters the flux through a second reaction by changing the value of a constraint on the second reaction. The function can correlate a constraint with at least one reaction, correspond to changes regulating a reaction (see paragraph 0049) or correspond to a regulatory event where the modifier of flux through a reaction includes an environmental condition such as time (see paragraph 0047). Because claims 35-37 further specify the origin of the condition-dependent value provided in step (c) of base claim 34, and because the application describes that a variable constraint can be derived from at least one reaction in the data structure or a regulatory or temporal event of the claimed invention, the claim as written it is clear and definite. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claim 41 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite allegedly for being further directed to a regulatory data structure. The Office asserts that the inclusion of the additionally claimed element is unclear and that the claim fails to set forth an additional positive, active step or modify and existing step. Claim 48 stands similarly rejected allegedly because further recitation of a constraint function fails to set forth an additional step or modify an existing step. Claim 41 is directed to the method of determining a systemic property of a biochemical reaction network of claim 34 and further includes a regulatory data structure. Claim 41 has been amended above to recite that the data structure of base claim 34 further includes the claimed regulatory data structure recited in claim 41. In light of this amendment, Applicants submit that the rejection is moot and respectfully request its withdrawal.

With respect to claim 48, directed to a constraint function that correlates an outcome of a regulatory event with the claimed variable constraint, Applicant respectfully draws the Office's

attention to the meaning of the term “variable constraint” as described previously with respect to claims 35-37 and as set forth at, for example, paragraph 0049. A variable constraint can assume any of a set of values in response to being acted upon by a function. Therefore, the variable constraint recited in claim 41 includes a function. Claim 48 further modifies this element by specifying that the function correlates an outcome of a regulatory event with the variable constrain. Accordingly, claim 48 sets forth an additional step or modifies an existing step and is clear and definite as written. Therefore, withdrawal of this ground of rejection is respectfully requested.

Claim 55 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for use of the term “modifying” allegedly because the claim is unclear as to what is modified, how it is modified or why it is modified. Applicants submit that claim 55 is clear and definite. The application describes at, for example, paragraph 0037 that a data structure corresponds to a representation of information in a format that can be manipulated. Thus, the claimed relationship of the plurality of reactants and reactions of the data structure wherein one of the reactions is a regulated reaction can be modified by manipulation.

Further, with respect to the claimed regulated reaction, the application describes at, for example, paragraph 0032 that such reactions experience an altered flux due to a change in the value of a constraint or a reaction that has a variable constraint. Similarly, paragraph 0047 describes, for example, that a data structure can be modified by a regulatory event which is a representation of a modifier of the flux through a reaction that is independent of the amount of reactants available to the reaction. Thus, regulated reactions of the claimed data structure can be modified by changing the value of a constraint or a reaction having a variable constraint. As described at, for example, paragraphs 0048 and 0049 a variable constraint can assume any of a set of values in response to being acted upon by a function and that implementation of such changes include, for example, changes that result from one or more reactions specified in the data structure, from a regulatory event or from a temporal event when acted on by a function that alters the flux through a second reaction by changing the value of a constraint on the second reaction. The function can correlate a constraint with at least one reaction, correspond to changes regulating a reaction or correspond to a regulatory event where the modifier of flux through a reaction includes an environmental condition such as time (see, for example,

paragraphs 0033 and 0047 - 0049). Thus, the application teaches and exemplifies modifications of a data structure or a constraint set that can be implemented using the methods of the invention and is clear as written. Withdrawal of this ground of rejection is respectfully requested.

Claim 64 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear how the claimed gene database modifies the method of base claim 34. In support, the Office alleges that the database is not involved in step (e) of claim 34.

Applicants submit that the claim is clear as written. Claim 64 is directed to providing a gene database relating one or more reactions in the claimed data structure of base claim 34 with one or more open reading frames or proteins. Claim 64 adds the additional requirement of relating gene or protein information with the claimed data structure relationship of a plurality of reactants and reactions. The application describes the inclusion of such an additional relationship in a data structure of the invention when it states:

Annotation and information that can be used in this embodiment of the invention includes the genome sequence, the annotation data, or regulatory data such as the location of transcriptional units or regulatory protein binding sites, as well as the biomass requirements of an organism. Such information can be used to construct essentially genomically complete data structures representing metabolic and regulatory genotypes. These data structures can be analyzed using mathematical methods such as those described above.

Application, para. 0086.

Therefore, the application describes, for example, that information obtained from a gene database can be included in a data structure of the invention to more completely represent a metabolic and regulatory phenotype. In light of this description as well as other teachings in the application, Applicants maintain that claim 64 is clear and definite and respectfully request withdrawal of this ground of rejection.

Claims 65 and 66 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it is unclear whether the identification of an open reading frame or a protein corresponds to the claimed systemic property. In this regard, the Office appears to allege that it is unclear whether these identification steps occur in step (e) or some other step of the claimed method. Similar to the previous rejection, claims 65 and 66 depend from claim 64, which adds the additional requirement of relating gene or protein information with the claimed

data structure relationship of a plurality of reactants and reactions. In this regard, Applicants draw the Examiner's attention to claim 64 which expressly states:

[P]roviding a gene database relating one or more reactions in said data structure with one or more open reading frames or proteins.

Application, claim 64 (emphasis added).

Therefore, the plain language of claim 64 and its dependents recite that the gene database information relates open reading frame or protein information in the claimed data structure. In light of this language, the claim recites with sufficient clarity that the open reading frame or protein information is used in the data structure of step (a). Therefore, the claims are sufficiently clear to satisfy the requirements of the second paragraph of § 112 and withdrawal of this ground of rejection is respectfully requested.

Claim 71 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because it fails to recite time limitations. The Office acknowledges that the application discloses determining a systemic property at a first and a second time but further alleges that the claim as written repeats the method steps rather than determines a systemic property at temporally distinct times. Claim 71 is directed to a method of determining a systemic property of a biochemical reaction network at a first and second time. The method includes determining at least one flux distribution at a first time to determine a systemic property at a first time, modifying the variable constraint and determining at least one flux distribution at a second time to determine a systemic property at a second time. Although clear as filed, claim 71 has been amended above to further recite that the flux distribution in step (g) is determined at a second time. Accordingly, this amendment renders the rejection moot and withdrawal is respectfully requested.

Claim 73 stands rejected under 35 U.S.C. § 112, second paragraph, for being indefinite allegedly because the term "change in an environmental condition" is unclear. The Office asserts that base claim 71 fails to recite any such condition. Applicants submit that the claim as written is properly supported in base claim 71. In this regard, claim 71 recites providing or modifying a condition-dependent value to a variable constraint. The application teaches that the

claimed value can be based on a variety of conditions, including environmental conditions, when it describes:

As used herein, the term “variable” when used in reference to a constraint is intended to mean capable of assuming any of a set of values in response to being acted upon by a function. . . . A function included in the term can also correlate a boundary value with an environmental condition such as time, pH, temperature or redox potential.

Application, para. 0049.

Therefore, the term “variable constraint” includes modifications in response to a function. That function can be based on a change in an environmental condition. Claim 73 is sufficiently clear to satisfy the requirements of the second paragraph of § 112 because it clearly recites that the variable constraint changes according to environmental conditions. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Priority

Priority of the claimed invention to either provisional application serial numbers 60/272,754, filed March 1, 2001, or 60/323,028, filed September 14, 2001, has not been accorded to the subject application. The Office simply asserts that the claimed computer readable medium or media or the methods of determining a systemic property are not disclosed in the priority applications and concludes that the subject application is entitled only to a filing date of March 1, 2002.

Applicants submit that all claims are entitled to priority as to the earliest filed provisional application. Applicants respectfully submit that the Office has failed to provide an adequate showing or sufficient reasons why the instant claims are not supported in either or both of the provisional applications to which priority is claimed. Mere conclusory statements that the “present claims is [*sic*] not disclosed in either provisional application” fails to provide a proper basis for lack of priority. Absent such a showing or reasoning, the Office has not satisfy its initial burden. Therefore, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1-3, 5-7, 17-20, 23-26, 29, 32-34, 40, 53-54, 56-61 and 64-66 stand rejected under 35 U.S.C. § 102(b) as anticipated by WO 00/46405 to Palsson. The Office alleges that WO 00/46405 describes a metabolic genotype for an organism including a stoichiometric matrix that can be analyzed to assess the effects under different metabolic constraints. The Office further alleges that the metabolic genotype includes regulated reactions and that flux balance analysis using linear programming can be employed for optimization where the constraints can be varied. Claim 1 is directed to a computer readable medium or media which includes a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network where at least one reaction is a regulated reaction and a constraint set having a variable constraint for the regulated reaction. Claim 34 is directed to a method for determining a systemic property of a biochemical reaction network. The method includes providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network where at least one reaction is a regulated reaction and a constraint set having a variable constraint for the regulated reaction. Similarly, claim 71 also is directed to a method for determining a systemic property of a biochemical reaction network and includes the additional step of determining a systemic property at a temporally distinct time.

When lack of novelty is based on a printed publication that is asserted to describe the same invention, a finding of anticipation requires that the publication describe all of the elements of the claims. *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, (Fed. Cir. 1998) (quoting *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544-45, 24 U.S.P.Q.2d 1133, 1136 (Fed. Cir. 1992)). To establish a *prima facie* case of anticipation, the Examiner must show that the single reference cited as anticipatory art describes all the elements of the claimed invention. The Office fails to particularly point out each of the elements claimed by in the invention that are allegedly described in WO 00/46405. Instead, the Office provides a cursory statement asserting that the cited reference anticipates the claimed invention. The abstract, figures, claims and pages 3 and 7-9 are generally pointed to in the Office Action as allegedly describing the recited elements of the claimed invention. However, none of these locations in the cited reference describe the invention as claimed.

For example, the invention claims a variable constraint for a regulated reaction, which is a reaction that experiences an altered flux due to a change in the value of a constraint or a reaction that has a variable constraint (see, for example, paragraph 0032). A variable constraint as been described previously and refers to a constraint that is capable of assuming any of a set of values in response to being acted upon by a function (see, for example, paragraph 0049). WO 00/46405 fails to describe at the cited passages a variable constraint for a reaction that experiences an altered flux due to a change in the value of a constraint or due to a constraint that is capable of assuming any of a set of values in response to being acted upon by a function. Instead, WO 00/46405 appears to describe a computational approach for assessing the effects of genetic deletions on the fitness of an organism and its ability to produce essential biomolecules required for growth.

Moreover, the Office neither provides a rational showing nor points to particular descriptions in WO 00/46405 that appear to show the steps of the claimed invention or each element claimed by the invention. In particular, Office has failed to show that WO 00/46405 describes computer readable medium or media or a method for determining a systemic property of a biochemical reaction network that includes a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network where at least one reaction is a regulated reaction and a constraint set having a variable constraint for the regulated reaction as claimed by the invention. Absent such a showing, the Office has not satisfied its burden. Therefore, the cited reference cannot anticipate the claimed invention and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-33 stand rejected under 35 U.S.C. § 103(a) as obvious over Edwards et al. The Office alleges that Edwards et al. describes a computer readable medium having a data structure and data and that the data required by the claimed invention is considered to be non-functional descriptive material, which does not make an obvious invention patentable.

To establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could

have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000), accord *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974) (to establish *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art); M.P.E.P. §2143.03.

The alleged obviousness rejection is based on the conclusion that the claimed relationships of the data structure and the claimed variable constraints correspond to non-functional descriptive material. However, and as described previously, the claimed data structure and variable constraints correspond to functional descriptive material because they consist of a physical or logical relationship among data elements which relate a plurality of reactants to a plurality of reactions of a biochemical network. Further, the claimed data structure and variable constraints also impart functionality when employed as a computer component because they are used to determine a systemic property of a biochemical network. Therefore, the Office has failed to make a *prima facie* showing that Edwards et al. describes each and every element of the invention as claimed.

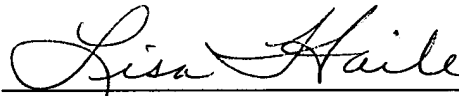
In particular, the Office neither provides a rational showing nor points to particular descriptions in Edwards et al. that appear to show each element of the claimed computer readable medium or media or methods of determining a systemic property of a biochemical reaction network. For example, the Office has failed to show that Edwards et al. describe a computer readable medium or media or a method for determining a systemic property of a biochemical reaction network that includes a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network where at least one reaction is a regulated reaction and a constraint set having a variable constraint for the regulated reaction as claimed by the invention. Absent such a showing, the Office has not satisfied its burden. Accordingly, Edwards et al. cannot render the invention of claims 1-33 obvious because all the elements of the claimed invention are not taught or suggested in the cited reference. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1-66 and 70-74 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved. The Commissioner is hereby authorized to charge any additional fees associated with the filing submitted herewith, or credit any overpayment, to Deposit Account No. 07-1896.

Respectfully submitted,

Date: April 1, 2005



Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213